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10/587,371	07/26/2006	Ho Sung Cho	AMBX-0028.00US	1687

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EXAMINER

SHAFFER, SHULAMITH H

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1647

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/587,371	Applicant(s) CHO ET AL.	
	Examiner SHULAMITH H. SHAFER	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 08 September 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-83 is/are pending in the application.
- 4a) Of the above claim(s) 1-43, 46-58 and 62-83 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 44, 45 and 59-61 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>papers 43-62, filed 4/24/09</u> . | 6) <input type="checkbox"/> Other: _____ |

Detailed Action

Status of Application, Amendments, And/Or Claims:

Applicants' amendment of 8 September 2009 is acknowledged. Claims 44 and 59-61 are amended and the amendment made of record.

Claims 1-83 are pending in the instant application. Claims 1-43, 46-58 and 62-83 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 44, 45, and 59-61 are under consideration, wherein the selector codon may be an amber, ochre or opal codon.

Information Disclosure Statement:

Applicants have filed twenty Information Disclosure statements (IDS) on the 24 April 2009. The Information Disclosure statements (IDS), 45-48, 50-52, 54-58, and 60-62 submitted on the 24 April 2009 have been considered. The signed copies are attached.

The information disclosure statement, document 49, filed 24 April 2009 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because reference 5 could not be found among the submissions of the instant invention. The information disclosure statement, document 53, filed 24 April 2009 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because reference 35 could not be found among the submissions of the instant invention. The information disclosure statement, document 59, filed 24 April 2009 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because references 30 and 44 could not be found among the submissions of the instant invention. These references have been lined through, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining

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compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Withdrawn Objections/Rejections

Applicants' amendment to the claims have overcome the following objections and rejections:

The objection to Claims 44 and 61 as reciting the acronym "4HB polypeptide"

The rejection of Claims 59 and 60 under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter

The rejection of Claim 61 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The rejection of Claims 44, 45, 59-61 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement

The rejection of Claims 44, 45 and 59-61 under 35 U.S.C. 112, first paragraph, scope of enablement

Maintained/New Grounds of Rejection

35 U.S.C. § 112, Second Paragraph:

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 44, 45, 59 and 60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 44, one of the independent claims of the instant invention, has been amended to recite “one selector codon that **efficiently and selectively** recognizes an orthogonal translation system....” (Emphasis added by Examiner). These terms, as recited in Claim 44, are relative terms and are not defined in the specification of the instant invention. Thus, the metes and bounds of the claim cannot be determined.

Claims 45, 59 and 60 are included in the rejection as dependent upon a rejected claim.

35 U.S.C. § 102:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The rejection of Claims 44, 45, and 59-61 rejected under 35 U.S.C. 102(e) as being anticipated Schultz et al. (US 2003/0082575, filed 10 April 2002, the ‘575 reference) is maintained for reasons of record and for reasons set forth below.

Claim 44, one of the independent claims of the instant invention, has been amended to recite “wherein the polynucleotide comprises at least one selector codon that efficiently and selectively recognizes an orthogonal translation system and wherein the 4HB polypeptide is chosen from the group consisting of human growth hormone, interferon, erythropoietin and granulocyte stimulating factor”. Claim 61, another independent claim of the instant invention has been amended to recite “wherein the 4HB polypeptide is chosen from the group consisting of human growth hormone, interferon, erythropoietin, and granulocyte cell stimulating factor comprising a

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ribosomally incorporated non-naturally encoded amino acid, wherein the non-naturally encoded amino acid has a ketone, alkyne or azide functional side group”

The ‘575 reference teaches an isolated nucleic acid comprising at least one selector codon [paragraph 0036], wherein the selector codon may be the amber codon [paragraph 0040]. The isolated nucleic acid encodes a therapeutic protein which may be an interferon, erythropoietin (EPO), G-CSF or human growth hormone [paragraph 0033]. The reference teaches a translation system comprising an orthogonal tRNA (O-tRNA) and an orthogonal aminoacyl tRNA synthetase (O-RS). Typically, the O-RS preferentially aminoacylates the O-tRNA with at least one unnatural amino acid in the translation system and the O-tRNA recognizes at least one selector codon. The translation system thus inserts the unnatural amino acid into a protein produced in the system, in response to an encoded selector codon [paragraph 0025]. Absent evidence to the contrary the polynucleotide comprising the selector codon efficiently and selectively recognizes an orthogonal translation system. Thus, the reference anticipates the limitations of claims 44 and 45.

The reference teaches a method of making the 4HB polypeptide recombinantly, utilizing a translation system comprising an orthogonal tRNA (O-tRNA) and an orthogonal tRNA synthetase and using the translation system to incorporate unnatural amino acids into protein [paragraph 0024]. The translation systems include cells, such as bacterial cells (e.g., *Escherichia coli*), archaeobacterial cells, eukaryotic cells (e.g., yeast cells, mammalian cells, plant cells, insect cells), thus reciting host cells comprising the nucleic acid, an orthogonal tRNA synthetase and orthogonal tRNA [paragraph 0026], and anticipating the limitations of claim 59 and 60. The reference teaches methods for producing at least one protein in a translation system such that the protein comprises at least one unnatural amino acid. In the methods, the translation system is provided with at least one nucleic acid comprising at least one selector codon, wherein the nucleic acid encodes the at least one protein, an orthogonal tRNA (O-tRNA), that functions in the translation system and recognizes the at least one selector codon and an orthogonal tRNA synthetase (O-RS) [paragraph 0036]. Among the side groups

present on the non-naturally encoded amino acids are ketones [paragraph 0155], azides or an alkyne functional side group [Claim 12]. Therefore, the limitations of claim 61 are also anticipated. The methods described may be used to generate large quantities of purified mutant proteins [paragraph 0097]; generating large quantities of the protein of interest would be considered an efficient and selective method.

Therefore, the teachings of the '575 reference anticipate all the limitations of claims 44, 45, and 59-61.

Applicants traverse the rejection (Response of 8 September 2009, page 13, 2nd paragraph). The reason for the traversal is:

Applicants believe that efficient incorporation presented in the instant application differs from that of previously filed application and have included claim amendments directed to this, as well as claims directed to specific side functional groups of the non-naturally encoded amino acids.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons:

As noted above, the '575 reference teaches non-naturally encoded amino acids comprising ketone, alkyne or azide functional side groups (paragraph 0115 and Claim 12).

Additionally, the arguments of counsel cannot take the place of evidence in the record. In the instant case the Applicants are asserting that the isolated nucleic acid encoding a four helical bundle wherein the polynucleotide comprises at least one selector codon of the instant invention comprises a system that efficiently and selectively recognizes an orthogonal translation system. The disclosure, asserts "This invention provides a highly efficient method for the selective modification of proteins with PEG derivatives, which involves the selective incorporation of non-genetically encoded amino acids, including but not limited to, those amino acids containing functional groups or substituents not found in the 20 naturally incorporated amino acids, including but not limited to a ketone, an azide or acetylene moiety, into proteins in response to a selector codon and the subsequent modification of those amino acids

with a suitably reactive PEG derivative” [paragraph 0215] and “In some embodiments, the non-naturally encoded amino acids include side chain functional groups that react efficiently and selectively with functional groups not found in the 20 common amino acids (including but not limited to, azido, ketone, aldehyde and aminooxy groups) to form stable conjugates [paragraph 0254]. However, applicants have presented no data, information, or teaching to support the assertion of unexpected, advantageous results or that the system of the instant invention provides more efficient or selective recognition of an orthogonal translation system than does the system taught in the prior art (the '575 reference) {see *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); and MPEP § 716.01(c)}.

The rejection is thus maintained.

The rejection of Claims 44, 45, and 59-61 under 35 U.S.C. 102(e) as being anticipated Chin et al. (US 2005/0009049, filed 16 April 2004, priority claimed to provisional applications 60/463,869 (filed 4/17/03), 60/479,931 (filed 6/18/03), 60//493,014 (filed 8/5/03) and 60/496,548 (filed 8/5/03), the '049 reference) is maintained for reasons of record and for reasons set forth below..

The '049 reference teaches a nucleic acid that comprises a polynucleotide that encodes a polypeptide of interest [paragraph 0016] which may be an interferon, erythropoietin (EPO), human growth hormone, and a G-CSF, which are all polypeptides disclosed as 4HB polypeptides by the specification of the instant invention [paragraph 0038]. The polynucleotide comprises a selector codon that is recognized by the O-tRNA. The selector codon may be a stop codon (e.g., an amber codon, an ochre codon, or an opal stop codon) [paragraph 0047]. Thus the limitations of claims 44 and 45 are anticipated.

The '049 reference teaches compositions of orthogonal tRNAs, orthogonal synthetases and pairs thereof, in eukaryotic cells and methods of producing proteins in eukaryotic cells that include unnatural amino acids [paragraph 0003]. The eukaryotic

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cell comprises an orthogonal tRNA synthetase (O-RS), an orthogonal tRNA (O-tRNA), and a nucleic acid that comprises a polynucleotide that encodes a polypeptide of interest [paragraph 0016]. The '049 reference teaches methods for producing, in a eukaryotic cell, at least one protein comprising at least one unnatural amino acid, thus anticipating the limits of claims 59 and 60. The methods include, growing, in an appropriate medium, a eukaryotic cell that comprises a nucleic acid that comprises at least one selector codon and encodes the protein of interest. The eukaryotic cell also comprises an orthogonal tRNA (O-tRNA) that functions in the cell and recognizes the selector codon and an orthogonal tRNA synthetase (O-RS) [paragraph 0042]. The reference teaches that the unnatural amino acids may include ketone containing amino acids [paragraph 0355], azide containing amino acids [paragraph 0356] and alkyne amino acids [paragraph 0366]. The reference also teaches purification of the recombinant proteins produced by the referenced methods [paragraph 0219]. Therefore, the limitations of claim 61 are also anticipated.

Absent evidence to the contrary, the nucleic acid taught by the '049 reference comprises a polynucleotide comprising a selector codon that efficiently and selectively recognizes an orthogonal translation system. Thus, the teachings of the '049 reference anticipates all the limitations of claims 44, 45, and 59-61.

Applicants traverse the rejection (Response of 8 September 2009, page 13, 3rd paragraph. The reason for the traversal is:

"Because Applicants' amendments to address the side functional groups and the efficiency of the orthogonal translation system, Applicants believe the presently amended claims overcome any and all objections and rejections"

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons:

As noted above, the '049 reference teaches that the unnatural amino acids may include ketone containing amino acids [paragraph 0355], azide containing amino acids [paragraph 0356] and alkyne amino acids [paragraph 0366], thus meeting the limitations of amended claim 61.

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Additionally, as stated above, the arguments of counsel cannot take the place of evidence in the record. In the instant case the Applicants are asserting that the isolated nucleic acid encoding a four helical bundle wherein the polynucleotide comprises at least one selector codon of the instant invention comprises a system that efficiently and selectively recognizes an orthogonal translation system (see discussion above). However, applicants have presented no data, information, or teaching to support the assertion of unexpected, advantageous results or that the system of the instant invention provides more efficient or selective recognition of an orthogonal translation system than does the system taught in the prior art (the '575 reference) {see *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965) and MPEP § 716.01(c)}.

The rejection is therefore maintained.

Conclusion:

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHULAMITH H. SHAFER whose telephone number is (571)272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D. can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shulamith H. Shafer/

Examiner, Art Unit 1647

/Gary B. Nickol /

Supervisory Patent Examiner, Art Unit 1646